IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Thorsten Heinzel	Examiner: AEDER, SEAN E
Serial No.: 10/528,104	Group Art Unit: 1642
Filed: SEPTEMBER 28, 2005	Confirmation Number: 3483

Title: **USE OF MOLECULAR MARKERS FOR THE PRECLINICAL AND CLINICAL PROFILING OF INHIBITORS OF ENZYMES HAVING HISTONE DEACETYLASE ACTIVITY**

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed June 30, 2008, attached herewith is Appellants' Brief on Appeal, pursuant to 37 CFR §41.37.

The Appeal Brief fee of $ 270.00 is filed/paid herewith.

This is an appeal from the decision of the Examiner finally rejecting claims 1-4, 6-10, 14, 22 and 28 of the above-identified application.

(I) REAL PARTY IN INTEREST

TOPO TARGET GERMANY AG, Frankfurt, GERMANY in conjunction with FORSCHUNGSZENTRUM KARLSUHE GMBH, Eggenstein-Leopoldshafen, GERMANY are the Assignees of Record of the entire right, title, and interest in and to the above-identified application, as recorded in the U.S. Patent and Trademark Office on March 17, 2006, at Reel/Frame 017693/0883.

(II) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(III) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-4, 6-10, 14, 22 and 28.
Claims objected to:	None.
Claims canceled:	Claim 23.
Claims allowed:	None.
Claims withdrawn:	Claims 5, 11-13, 15-21, 24-27.
Claims on Appeal:	Claims 1-4, 6-10, 14, 22 and 28 (Copy of claims on appeal in attached Appendix).

(IV) STATUS OF AMENDMENTS

After the Final Rejection of January 28, 2008, a Reply containing claim amendments was filed on April 28, 2008. In the Advisory Action mailed May 23, 2008, the Examiner indicated that the amendments would be entered for purposes of this appeal. Thus, the amendments presented with the After-Final Reply of April 28, 2008 are entered and are reflected in the claims on appeal shown in the attached Appendix of Claims.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

One embodiment of Appellants' invention (independent claim 1) is directed to a method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, wherein said HDAC inhibitor or potential HDAC inhibitor is a molecule which inhibits the enzymatic activity of said HDAC, comprising determining in a sample the amount of a molecular marker which is HDAC protein, wherein the sample is derived from cells which have been treated with said HDAC inhibitor or potential HDAC inhibitor, and wherein a change in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor. See, for example, page 5, paragraphs 2–4 of the originally-filed specification. See also, the paragraph bridging pages 12 and 13 of the originally-filed specification (for "enzymatic activity") and page 1, ¶1 and page 2, lines 3–5 of the originally-filed specification.

Claims 2–4, 6–10, 14 and 28 are either directly or indirectly dependent on independent claim 1. Dependent claim 2 recites that the the molecular marker is HDAC-2 protein (see, page 5, ¶3; under the "RESULTS" section of page 22; and the disclosure contained in, for example, Fig. 10 for support). Claim 3 recites that the sample is derived from a tissue affected by a disorder. See, page 6, lines 17–18. Claim 4, which is dependent on claim 3, recites that the disorder is skin cancer, melanoma, estrogen receptor-dependent and independent breast cancer, ovarian cancer, prostate

cancer, renal cancer, colon and colorectal cancer, pancreatic cancer, head and neck cancer, small cell and non-small cell lung carcinoma, leukemias and other types of blood cell cancer or an endocrine disease based on aberrant recruitment of histone deacetylase. See, for example, page 6, last paragraph and page 7, ¶1 of the originally-filed specification. Claim 6 recites a method of detection of the molecular marker using antibody molecules. See, page 8, ¶1. Claim 7, which depends on claim 6, recites methods for antibody-based detection of such markers, such as, for example, Western Blotting, ELISA, immunohistochemistry and/or flow cytometry. See, for example, the paragraphs bridging page 8, last paragraph to page 9, ¶3 of the originally-filed specification. Claim 8 recites an additional element of selecting an inhibitor based on the modulation of the expression of the molecular marker. See, for example, page 10, lines 6–10. Claim 9 recites the use of a reference sample, wherein the reference sample is derived from cells which have not been treated with said HDAC inhibitor or potential HDAC inhibitor. See, for example, page 10, lines 16–19. Claim 28 is supported, at least, by the disclosure contained in page 1, ¶1 and page 2, lines 3–5 of the originally-filed specification (i.e., "enzymes having histone deacetylase activity" carry out "removal of acetyl groups").

Another embodiment of Appellants' invention (independent claim 10) relates to a method for profiling histone deacetylase (HDAC) inhibitors or potential HDAC inhibitors, comprising contacting a cell with an HDAC inhibitor or potential HDAC inhibitor; determining the amount of a molecular marker which is HDAC protein in the presence and absence of said inhibitor; and creating a profile of said HDAC inhibitor or potential HDAC inhibitor based on its ability to down-regulate the expression of said molecular marker which is HDAC protein. See, for example, page 11, 1st paragraph and page 13, ¶3 (lines 12–14 at page 13) of the originally-filed specification. Claim 14 directly depends on independent claim 10. Claim 14 is directed to the use of antibody molecules directed against HDAC-2 protein. See, page 8, ¶1 and the disclosure contained in Example 2.

Yet another embodiment of Appellants' invention (independent claim 22) is drawn to a method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, comprising contacting a cell with a test compound and measuring the level(s) of a molecular marker which is HDAC protein, wherein a reduction in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor. Support for claim 22 can be found in, for example, the disclosure contained in Example 2 of the originally-filed specification.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants request a review of the following remaining grounds of rejection:

(1) The rejection of claims 1-4, 6-10, 14, 22 and 28 under 35 U.S.C. §102(b) as allegedly being anticipated by MacLeod (WO 00/71703);

(3) The rejection of claim 28 under 35 U.S.C. §112, ¶1, due to allegedly reciting new matter.

Grouping of claims

Claims 1-4, 6-10, 14 and 22, on appeal, are grouped together and stand or fall together with respect to the anticipation rejection under 35 U.S.C. §102(b).

The merit(s) of claim 28 with respect to the anticipation rejection is addressed separately.

The new matter rejection is addressed separately from the anticipation rejection.

(VII) ARGUMENT

(1) Rejection under §102(b)

Claims 1-4, 6-10, 14, 22 and 28 on appeal, are not anticipated by MacLeod (WO 00/71703). The rejection thereof under 35 U.S.C. §102(b) is not supported on the record as a whole and should be reversed.

MacLeod is drawn to inhibition of HDAC at the nucleic acid level. See, page 3, lines 2–5 of MacLeod et al. Example 2 of MacLeod discloses inhibition of HDAC activity using "antisense oligonucleotides." At page 8 of the Office Action mailed May 16, 2007 the Examiner concedes that "MacLeod further teaches a method wherein the inhibitors are further selected by their ability to inhibit the expression of HDAC-2 polypeptide (emphasis added)." The Examiner's arguments in the Final Office Action mailed January 28, 2008 are in *ipsis verbis* to the arguments presented in the non-final Office Action. As such, the Final Office Action and the subsequent Advisory Action have both failed to address the merits of Appellants' arguments, for example, the difference between inhibition of protein *expression* vs. inhibition of protein *activity*, which is explicitly recited in the claims.

The Examiner's error below is in failing to properly interpret the claim term "a molecule which inhibits the enzymatic activity of said HDAC (histone deacetylase)."

The disclosure in MacLeod's Example 3, which the Office Action relies on in levying the anticipation rejection, teaches the use of "second generation antisense oligonucleotides (emphasis added)." According to MacLeod, such second generation oligonucleotides, which comprise "phosphothionate linkers," are allegedly more stable than those anti-sense molecules utilized in Example 2 of the reference. See, Example 3 of the cited WO 00/71703. The reference fails to teach any inhibitor, let alone an HDAC inhibitor. For example, in the 2nd paragraph of Example 3, MacLeod explicitly states that antisense molecules are capable of inhibiting *protein expression*. The

reference does not teach an HDAC inhibitor or potential HDAC inhibitor which is a molecule that inhibits the enzymatic activity of said HDAC. As such, MacLeod cannot anticipate what is claimed by the instant invention. Furthermore, a skilled artisan will appreciate that MacLeod's method of genetic manipulation of protein expression (using antisense technology) is fundamentally different from Applicants' disclosed technique of modulation of *enzyme activity* using inhibitors. For example, the pharmacological differences between the two approaches, both at the molecular and the physiological level, are well-recognized in the art. See the enclosed Exhibit A, which were presented in the Reply filed April 28, 2008.

Applicants' claims are directed to a method of characterization of an HDAC inhibitor or a potential HDAC inhibitor comprising measuring the amount of markers such as HDAC. As described in the instant specification and the Examples contained therein, the method comprises the characterization of an inhibitor which modulates the *enzymatic activity* of HDAC. There is no mention in MacLeod that such antisense molecules, which modulate protein levels, could be characterized in a manner recited in the present method claims. Furthermore, the cited reference is also totally silent with respect to profiling histone deacetylase (HDAC) inhibitors or potential HDAC inhibitors based on the ability thereof to down-regulate the expression of said molecular marker which is HDAC protein. See, instant claim 10.

Since all material elements of the claims are not disclosed in the cited reference, the teachings of MacLeod cannot anticipate or render obvious the methods taught by the instant invention. Thus, the present invention is not anticipated by MacLeod et al.

With respect to present claim 28, in the paragraph bridging pages 5 and 6 of the Office Action mailed January 28, 2008, the Examiner alleges that "HDAC inhibitor or potential HDAC inhibitor (i.e., antisense oligonucleotide) taught by MacLeod et al., which inhibits HDAC expression *would* interfere with the catalytic activity of HDAC since a lack of HDAC would result in a lack of HDAC catalytic activity." Insofar as the Office Action fails to provide *any* evidence (for example, scientific publications or other evidentiary documents) supporting this contention, the rejection is without legal merit. Moreover, Appellants submit that the Examiner's contention that high level of proteins is equivalent to high level of enzyme activity is largely misplaced. It is well known in the art that *activity* and *levels* of enzymes are two separate aspects of enzyme kinetics. A basic review of any standard biochemistry textbook can be used to verify this. Withdrawal of the rejection is respectfully requested.

All the rejections should therefore be withdrawn.

(2) Rejection under 35 U.S.C. §112, ¶1

The Advisory Action mailed May 23, 2008 did not address Appellants' arguments against the rejection of claim 28 under this section. As such, the "new matter" rejection is respectfully traversed. It is submitted that the specification, for example, the paragraph bridging pages 12 and 13, provides explicit support for the claimed subject matter. See, "enzymatic activity." See also, page 1, ¶1 and page 2, lines 3–5 of the originally-filed specification for a description of said activity (i.e., "enzymes having histone deacetylase activity" carry out "removal of acetyl groups"). For the reasons discussed above, Appellants respectfully submit that the rejection of claim 28 under 35 U.S.C. § 112, ¶1 is misplaced. Withdrawal of this rejection is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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(VIII) CLAIMS APPENDIX

Claim 1. A method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, wherein said HDAC inhibitor or potential HDAC inhibitor is a molecule which inhibits the enzymatic activity of said HDAC, comprising

determining in a sample the amount of a molecular marker which is HDAC protein,

wherein the sample is derived from cells which have been treated with said HDAC inhibitor or potential HDAC inhibitor, and

wherein a change in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor.

Claim 2. A method according to claim 1 wherein the molecular marker is HDAC-2 protein.

Claim 3. A method according to claim 1 wherein the sample is derived from a tissue affected by a disorder.

Claim 4. A method according to claim 3 wherein the disorder is skin cancer, melanoma, estrogen receptor-dependent and independent breast cancer, ovarian cancer, prostate cancer, renal cancer, colon and colorectal cancer, pancreatic cancer, head and neck cancer, small cell and non-small cell lung carcinoma, leukemias and other types of blood cell cancer or an endocrine disease based on aberrant recruitment of histone deacetylase.

Claim 6. A method according to claim 1 wherein the amount of the molecular marker is determined by use of an antibody directed against the molecular marker.

Claim 7. A method according to claim 6 wherein the amount of molecular marker is determined by Western Blotting, ELISA, immunohistochemistry and/or flow cytometry.

Claim 8. A method according to claim 1 further comprising the step of selecting the inhibitor if it has the activity of modulating the expression of the molecular marker.

Claim 9. A method according to claim 1 further comprising the step of determining in a reference sample the amount of said molecular marker wherein the reference sample is derived from cells which have not been treated with said HDAC inhibitor or potential HDAC inhibitor.

Claim 10. A method for profiling histone deacetylase (HDAC) inhibitors or potential HDAC inhibitors, comprising

contacting a cell with an HDAC inhibitor or potential HDAC inhibitor;

determining the amount of a molecular marker which is HDAC protein in the presence and absence of said inhibitor; and

creating a profile of said HDAC inhibitor or potential HDAC inhibitor based on its ability to down-regulate the expression of said molecular marker which is HDAC protein.

Claim 14. The method according to claim 10 comprising employing an antibody directed against HDAC-2 protein.

Claim 22. A method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, comprising

contacting a cell with a test compound and

measuring the level(s) of a molecular marker which is HDAC protein,

wherein a reduction in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor.

Claim 28. The method according to claim 1 wherein the HDAC inhibitor or potential HDAC inhibitor interferes with the enzymatic activity of said HDAC.

(IX) EVIDENCE APPENDIX

Appendix of evidence submitted pursuant to §§ 1.130, 1.131, or 1.132 of this title or of any other evidence entered by the Examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered in the record by the Examiner. Copies of the evidentiary documents are attached.

Reference/Exhibits	Entered in the Record
1. "Antisense RNA" (Wikipedia article)	Filed by appellants with After Final Reply of April 28, 2008; Reference entered. See, "Notes" section at page 2, ¶1 of the Advisory Action mailed May 23, 2008.

(X) RELATED PROCEEDINGS APPENDIX

(None)